PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION See Form PCT/IPEA/416	
72739-76931		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/SE2004/001209	18.08.2004	18.08.2003
International Patent Classification (IPC) or national classification and IPC		
A01K 67/027		
Applicant		
BETAGENON AB et al		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 9 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *(sent to the applicant and to the International Bureau)* a total of 2 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s))
      _____ , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:
   - ☒ Box No. I Basis of the report
   - ☒ Box No. II Priority
   - ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☐ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☒ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☒ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
15.06.2005	22.09.2005
Name and mailing address of the IPEA/SE Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Facsimile No. +46 8 667 72 88	Authorized officer Terese Sandström / MRo Telephone No. +46 8 782 25 00

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/SE2004/001209

Box No. I Basis of the report

1. With regard to the **language**, this report is based on:

☒ the international application in the language in which it was filed

☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of:

- ☐ international search (Rules 12.3(a) and 23.1(b))
- ☐ publication of the international application (Rule 12.4(a))
- ☐ international preliminary examination (Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

☐ the international application as originally filed/furnished

☒ the description:

pages 1-19 as originally filed/furnished
pages* _____ received by this Authority on _____
pages* _____ received by this Authority on _____

☒ the claims:

pages _____ as originally filed/furnished
pages* _____ as amended (together with any statement) under Article 19
pages* 20-21 received by this Authority on 15.06.2005
pages* _____ received by this Authority on _____

☒ the drawings:

pages 1-7 as originally filed/furnished
pages* _____ received by this Authority on _____
pages* _____ received by this Authority on _____

☒ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages _____
- ☐ the claims, Nos. _____
- ☐ the drawings, sheets/figs _____
- ☐ the sequence listing *(specify)*: _____
- ☐ any table(s) related to the sequence listing *(specify)*: _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

- ☐ the description, pages _____
- ☐ the claims, Nos. _____
- ☐ the drawings, sheets/figs _____
- ☐ the sequence listing *(specify)*: _____
- ☐ any table(s) related to the sequence listing *(specify)*: _____

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/SE2004/001209

Box No. II Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

   ☐ copy of the earlier application whose priority has been claimed (Rule 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 66.7(b)).

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rule 64.1). Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

The priority was considered valid for the aspects disclosed in WO 03068959 A1. Therefore, this document is not disclosed in the statement in Box V.

Box No. V **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1-9	YES
	Claims		NO
Inventive step (IS)	Claims	1-9	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-9	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

Documents cited in the International Search Report:
D1: WO 0176361 A1
D2: WO 02057783 A3
D3: Itoh Y. et al., "Free fatty acids regulate insulin secretion from pancreatic beta cells through GPR40", Nature, 13 March 2003, Vol. 422, No. 6928, pages 173-176
D4: Briscoe C.P. et al., "The Orphan G Protein-Coupled Receptor GPR40 Is Activated by Medium and Long Chain Fatty Acids", The Journal of Biological Chemistry, 28 March 2003, Vol. 278, No. 13, pages 11303-11311

The present application relates to a transgenic animal model over-expressing GPR40 under the control of the Ipf1/Pdx1 promoter. This animal model mimics diabetes type 2 and can be used to develop therapies against the disease.

D1 discloses a transgenic diabetes type 2 model laboratory animal, e.g. a mouse, which expresses a dominant negative form of FGFR1c under the control of the Ipf1/Pdx1 promoter. (Abstract; page 1, lines 5-14; page 4, lines 6-14; examples 1-6.)

D1 is considered to disclose the closest prior art.

The transgenic animal claimed in claims 1-3 differs from the transgenic mouse disclosed in D1 due to the use of GPR40 instead of a dominant negative form of FGFR1c for inducing diabetes.

This difference has not been shown to give rise to any unexpected technical effect.

.../...

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of: Box V

Thus, the problem solved is merely to provide an alternative diabetes type 2 animal model. This has, by the applicants, been achieved by over-expressing GPR40.

D2, which is based on published studies in D3, suggests a connection between GPR40 and diabetes type 2.

Experiments in D2 and D3 show that GRP40 is expressed in pancreas, more precisely in insulin-producing beta-cells. It was also shown that GRP40 is upregulated in a rodent model of obesity and insulin-resistance. Expression of GRP40 in whole pancreas of ob/ob mice, which are obese, hyperglycaemic, and insulin-resistant and exhibit beta-cell hyperplasia, was increased. This increase in GRP40 may be due in part to the increased beta-cell number manifest in the pancreas of the animal model. Both D2 and D3 speculate that agonists of GRP40, i.e. activation of GRP40, might stimulate glucose-induced insulin-secretion. D2 also suggests a role for antagonists of GRP40, i.e. inhibition of GRP40, in reducing lipotoxicity of fatty acid and thereby improve beta-cell function. Neither D2 nor D3 disclose any in vivo experiments. Hence any effects of overexpression/activation or downregulation/inhibition of GRP40 in in vivo systems has not been shown. The function of activation/inactivation of GRP40 in vivo is merely based on speculations. In addition, in view of the information given in D2 and D3, it would rather lead a person skilled in the art to the assumption that overexpression of GRP40 would lead to the opposite effect than the one shown in the present application.

(D2: Page 4, lines 7-16; page 6, lines 15-16; page 7, lines 1-13; page 8, lines 9-12; page 17, line 29-page 18, line 12; page 20, lines 4-6; examples 2-4; claims 24 and 27-28; D3: abstract; page 11305, column 2 paragraph 4-page 11307, column 2, paragraph 2; page 11309, column 2, paragraph 3; page 11310, column 1, paragraph 2-column 2, paragraph 2.)

Thus, for a person skilled in the art, who wishes to solve the problem state above, to overexpress GRP40 does not seem to lie close to hand. Consequently the subject matter claimed in claims 1-3 is considered to involve an inventive step.

Consequently, the methods as claimed in claims 4-9 is also considered to involve an inventive step.

D4 is considered to disclose the general state of the art.

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**

Continuation of: Box V

To summarise, the subject matter claimed in claims 1-9 is novel and is considered to involve an inventive step. The subject matter claimed in claims 1-9 is considered to be industrially applicable.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/SE2004/001209

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

Application No. Patent No.	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date (valid claim) *(day/month/year)*
WO03068959 A1	21.08.2003	13.02.2003	14.02.2002 12.07.2002 12.11.2002 22.01.2002

2. Non-written disclosures (Rule 70.9)

Kind of non-written disclosure	Date of non-written disclosure *(day/month/year)*	Date of written disclosure referring to non-written disclosure *(day/month/year)*

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

In some countries, general claims on transgenic animals, such as claim 1, are not allowable due to moral aspects. See e.g. the decision of the Opposition Division from 2001-11-07 regarding application EP0169672.

Supplemental Box Relating to Sequence Listing

Continuation of Box No. I, item 2:

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this report was established on the basis of:

   a. type of material

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material

   ☒ on paper

   ☒ in electronic form

   c. time of filing/furnishing

   ☒ contained in the international application as filed

   ☒ filed together with the international application in electronic form

   ☐ furnished subsequently to this Authority for the purposes of search and/or examination

   ☐ received by this Authority as an amendment* on _____

2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

* *If item 4 in Box No. I applies, the listing and/or table(s) related thereto, which form part of the basis of the report, may be marked "superseded."*

Claims

1. A transgenic non-human laboratory animal over-expressing GPR40 comprising the promotor *Ipf1/Pdx1* for controlling the expression of GPR40.

2. The transgenic animal of claim 1, wherein the animal is a rodent.

3. The transgenic animal of claim 2, wherein the animal is a mouse or a rat.

4. A method for testing whether a chemical compound possessing a certain effect for treating diabetes Type 2 using a transgenic laboratory animal comprising the steps of:
a) providing a chemical compound to be tested;
b) providing a transgenic laboratory animal according to claim 1;
c) exposing said animal to said chemical compound; and
d) determining whether said chemical compound has an effect on the blood glucose level in said animal.

5. A method for testing whether a chemical compound possessing a certain effect for treating diabetes Type 2 using a transgenic laboratory animal comprising the steps of:
a) providing a chemical compound to be tested;
b) providing a transgenic laboratory animal according to claim 1;
c) exposing said animal to said chemical compound; and
d) determining whether said chemical compound has an effect on the triglyceride level in said animal.

6. A method for testing whether a chemical compound possessing a certain effect for treating diabetes Type 2 using a transgenic laboratory animal comprising the steps of:
a) providing a chemical compound to be tested;

b) providing a transgenic laboratory animal according to claim 1;
c) exposing said animal to said chemical compound; and
d) determining whether said chemical compound has an effect on the low density lipoprotein (LDL) level in said animal.

7. A method for testing whether a chemical compound possessing a certain effect for treating diabetes Type 2 using a transgenic laboratory animal comprising the steps of:
a) providing a chemical compound to be tested;
b) providing a transgenic laboratory animal according to claim 1;
c) exposing said animal to said chemical compound; and
d) determining whether said chemical compound has an effect on the high density lipoprotein (HDL) level in said animal.

8. A method for testing whether a chemical compound possessing a certain effect for treating diabetes Type 2 using a transgenic laboratory animal comprising the steps of:
a) providing a chemical compound to be tested;
b) providing a transgenic laboratory animal according to claim 1;
c) exposing said animal to said chemical compound; and
d) determining whether said chemical compound has an effect on the free fatty acids in said animal.

9. A method for testing whether a chemical compound possessing a certain effect for treating diabetes Type 2 using a transgenic laboratory animal comprising the steps of:
a) providing a chemical compound to be tested;
b) providing a transgenic laboratory animal according to claim 1;
c) exposing said animal to said chemical compound; and
d) determining whether said chemical compound has an effect on the glucose tolerance content in said animal.